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(71) Applicant *(for all designated States except US)*: WEST PHARMACEUTICAL SERVICES DRUG DELIVERY & CLINICAL RESEARCH CENTRE, LTD. [GB/GB]; Albert Einstein Centre, Nottingham Science & Technology Park, University Boulevard, Nottingham NG7 2TN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DAVIS, Stanley, Stewart [GB/GB]; 19 Cavendish Crescent North, The Park, Nottingham NG7 1BA (GB). WATTS, Peter, James [GB/GB]; Flat 2, 47 Highfield Road, West Bridgford, Nottingham NG2 6DR (GB). CHENG, Yu-Hui [GB/GB]; 44 Leamington Drive, Chilwell, Nottingham NG9 5LN (GB).

(74) Agent: DEE, Ian; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

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(57) Abstract

The present invention provides a composition comprising (i) an immunosuppressant, (ii) at least one compound selected from tocopherol, tocotrienol and the derivatives thereof, (iii) a short chain phospholipid and (iv) a non–ionic surfactant. The immunosuppressant is preferably cyclosporin.

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ORAL FORMULATION

The present invention relates generally to oral formulations of immunosuppressants. More specifically, the present invention relates to oral formulations of cyclosporin.

Cyclosporin is a fungal metabolite and potent immunosuppressant. It can also be used as an anti-inflammatory agent and anti-parasitic agent. It has found to be of particular use in the field of organ and tissue transplantation, for prevention of graft rejection following bone marrow, kidney, liver, pancreas, heart and heart-lung transplantation, and for prophylaxis of graft-versus-host disease. It is a cyclic, poly-N-methylated undecapeptide and is very insoluble in aqueous media.

Oral and parenteral formulations of cyclosporin are known. However, there are certain disadvantages associated with the oral formulations of cyclosporin that are currently known. For example, when cyclosporin is administered orally the bioavailability of the cyclosporin is both low and variable.

Vonderscher and Meinzer (Trans. Proc. 26, 2925-2927 (1994)) define some criteria for an optimal oral formulation of a cyclosporin, namely:

Criterion 1: The formulation should release cyclosporin very quickly in the gastrointestinal tract in order to use the entire length of its limited absorption window. Vonderscher and Meinzer indicated that this is most probably only achievable with a liquid formulation.

Criterion 2: The formulation should allow cyclosporin to be kept in solution during the dilution by aqueous gastrointestinal fluids along its absorption window (no precipitation).

Criterion 3: The formulation should be able to incorporate a high concentration of cyclosporin in a dissolved and stable state over a long period of time without recrystallisation and with a minimal amount of acceptable excipients. For example, a dose of 5 mg/kg per day with a 10% drug loading in the formulation would mean a daily intake of more than 3 g of excipients.

Criterion 4: The biological processing of the formulation should be as independent as possible of the physiological state of the gastrointestinal tract (no bile or pancreatic juice dependence, no food effect, etc.).

Nobe and Markham (Drug, 50, 924-941 (1995)) reviewed the pharmacokinetic properties, clinical efficacy and tolerability of oral cyclosporin formulations and attributed the low and variable bioavailability of orally administered cyclosporin to poor absorption.

However, Wu et al. (Clin. Pharm. Ther. 58, 492, 1995) indicated that in the absence of intestinal metabolism, cyclosporin absorption can be as high as 86% from commercially available products.

The absorption of cyclosporin in the intestines can be affected by cytochrome P4503A4 metabolism within small intestine epithelial cells as well as P-glycoprotein efflux, a versatile xenobiotic pump (Walkins,

Advan. Drug Del. Rev. 27, 161-170, 1997). The P-glycoprotein content of the large bowel is a likely explanation for the reduced bioavailability associated with distal administration of cyclosporin (Thummel et al., Adv. Drug Dev. 27, 99-127, 1997).

WO-95/20980 describes a method for increasing the bioavailability of orally administered hydrophobic compounds such as cyclosporins which comprises using an inhibitor of cytochrome P4503A4 enzyme or an inhibitor of P-glycoprotein mediated membrane transport.

There are many examples of oral cyclosporin formulations in the prior art. These are generally based on lipid vehicles, surfactants that are often mixed with alcohols and propylene glycol, or polyethylene glycols or ethoxylated triglycerides.

For example, the licensed cyclosporin formulation Neoral™ (Novartis, Switzerland) contains cyclosporin together with DL-α tocopherol (as an oxidant), absolute alcohol, propylene glycol, corn oil mono-di-triglyceride and polyoxyl 40 hydrogenated castor oil (ABPI Data Sheet Compendium, 1996/7, ABPI, London, Sandoz Pharmaceuticals).

The original cyclosporin product Sandimmune™ from Sandoz Pharmaceuticals (Switzerland) contains cyclosporin together with corn oil and a surfactant as a dispersing agent (corn oil polyoxyl-6 esters).

A range of patents and patent applications refer specifically to oral cyclosporin formulations and these will now be discussed briefly.

GB-2,270,842 describes a composition comprising (i) cyclosporin, (ii) a hydrophilic organic solvent, e.g. polyoxyl-stearate glycolfurol, ethyl acetate, propylene glycol, lower alkanols or mixtures thereof, (iii) mixed mono-, di- and triglycerides or transesterified and polyethoxylated vegetable oil, e.g. Labrafil or Maisine, and (iv) a polyoxyethylene sorbitan fatty acid ester surfactant.

GB-2,222,770 describes a composition comprising (i) cyclosporin, (ii) a hydrophilic component, e.g. transcutol, glycofurol or 1,2 propylene glycol, (iii) a lipophilic component, e.g. capric/caprylic triglyceride, a glycerylstearate, triglyceride, triglyceryl oleate or propylene glycol fatty acid, and (iv) a surfactant which can be hydrophilic, e.g. polyoxyl castor oil polyoxyl-stearate, poloxamer, lecithins and bile salts, or hydrophobic, e.g. corn oil PEG esters glycerylcopyrate, sorbitan laurate, oleate or palmitate and glyceryl monooleate derivatives.

GB-2,257,359 describes a composition comprising cyclosporin with (i) 1,2 propylene glycol, (ii) mixed mono-, di- and triglycerides, and (iii) a hydrophilic surfactant.

WO-97/07787 describes a composition comprising cyclosporin with (i) at least one C_{2-3} alkanol solvent, (ii) at least one non-ionic polyoxyalkylene surfactant, e.g. a polyoxyethylene alkyl ester or a polyoxyethylene sorbitan fatty acid ester, and (iii) one or more additional co-solvents such as a fatty acid ester, e.g. ethyl oleate or isopropyl myristate, or a diol, e.g. PEGs.

WO 95/06464 describes a formulation comprising cyclosporin with ethanol, 1,2 propyleneglycol, glycerine, polyethylene glycol 300, polyethylene glycol 400, benzylalcohol and a medium chain triglyceride or a plant oil.

DE-4,322,826 describes a composition comprising cyclosporin together with (i) at least one polyglycerine fatty acid ester and/or at least one sorbitan fatty ester, (ii) at least one conventional pharmaceutical and containing a triglyceride as a lipophilic component, and (iii) at least one non-ionic surfactant with a Hydrophilic-Lipophilic Balance (HLB) Value of at least 10.

DE-4,418,115 describes an emulsion or microemulsion pre-concentrate consisting of (i) a reaction product of castor oil and ethylene oxide, (ii) a mono-, di- and triglyceride of linoleic acid and oleic acid and/or a polyalkylated plant oil, (iii) propylene glycol, and (iv) ethanol.

WO-97/19692 describes a composition comprising cyclosporin with (i) at least one monoester of at least one saturated hydroxy fatty acid with polyethyleneglycol, and optionally (ii) a mono- or di-functional C_{2-3} alcohol, (iii) a mono-, di- and/or tri-ester of a fatty acid, and (iv) ricinoleic acid glyceride and small amounts of various unsaturated fatty acid glycerides or castor oil.

CH-641356 describes a formulation containing a cyclosporin and a carrier. The carrier consists of at least one of (i) a transesterification product of a triglyceride with a polyalkylene glycol, (ii) a saturated fatty

acid triglyceride, or (iii) a mono- or di-glyceride. The cyclosporin can only be cyclosporin A if the formulation is a solution for drinking which contains the esterification product of triglycerine oleate with a polyethylene glycol as component (i) and also contains olive oil or corn oil and ethanol.

GB-2,230,440 (DE-4,003,844) describes pharmaceutical compositions containing (i) a cyclosporin, (ii) a fatty acid saccharide monoester, and (iii) a diluent or carrier.

GB-2,228,198 describes a pharmaceutical composition that comprises a cyclosporin in a carrier medium comprising (i) a fatty acid triglyceride, (ii) a glycerol fatty acid partial ester or propylene glycol or sorbitol complete or partial ester, and (iii) a surfactant having an HLB of at least 10.

WO-97/03651 describes how Vitamin E can be used to solubilize drugs such as cyclosporin.

Many of the above formulations contain a number of synthetic pharmaceutical excipients and may also contain ethanol and/or propylene glycol. Neither alcohol nor propylene glycol is an ideal excipient since both are liquid and associated with side effects. Furthermore, the systems are complicated to process and are problematic when attempting to produce a conventional dosage form, such as a product contained in a hard gelatin or starch capsule, since the alcohol or propylene glycol decreases the stability of the capsule.

The present applicant has developed a new oral formulation of an immunosuppressant, such as a cyclosporin. The formulation may provide for quick release of the immunosuppressant into the gastrointestinal tract and may allow the immunosuppressant to be kept in solution during the dilution by aqueous gastrointestinal fluids. Moreover, the formulation may incorporate a high concentration of the immunosuppressant in a dissolved and stable state over a long period of time without recrystallisation and with a minimal amount of excipients.

According to the present invention, there is provided a composition for oral administration comprising (i) an immunosuppressant, e.g. cyclosporin, (ii) tocopherol (Vitamin E), tocotrienol or a derivative thereof, (iii) a short chain phospholipid, and (iv) a non-ionic surfactant.

In the composition of the invention, the tocopherol, tocotrienol or derivative thereof, the short chain phospholipid, and the non-ionic surfactant together function as a carrier system or excipient for the immunosuppressant.

The composition of the invention can provide for good solubility of the immunosuppressant, e.g. cyclosporin, in the excipient mixture as well as good dispersibility when placed in an aqueous environment.

The non-ionic surfactant can aid dispersion in an aqueous environment as well as reduce P-glycoprotein efflux in the gastrointestinal tract.

Immunosuppressive agents suitable for use in the present composition include cyclosporin and analogues and derivatives thereof, FK-506 (isolated from a species of streptomyces) and rapamycin (a product of the fungus streptomyces hygroscopicus) and analogues or derivatives thereof. Mixtures of immunosuppressive agents may be used if desired. Especially preferred immunosuppressants are the cyclosporins which are a group of cyclic oligopeptides produced by fungi. Suitable cyclosporins include cyclosporin A, cyclosporin B, cyclosporin C, cyclosporin D and cyclosporin G. Cyclosporin A is the principal form of cyclosporin.

The nomenclature for Vitamin E and related compounds is not unequivocal in current practice and can vary when used by different compendia and organisations. This problem has been well addressed by Sheppard et al. in Vitamin E in Health and Disease, Editors Packer, L. and Fuchs, J. Dekker, New York 1993 p.9.

The United States Pharmacopoeia described Vitamin E as a form of α-tocopherol. This includes d- or d, l-α-tocopherol acetate and d- or d, l-α-tocopherol succinate. The term Vitamin E is also used as a generic description for all tocopherol and tocotrienol derivatives that exhibit Vitamin E activity. Thus, the term tocopherol is not only synonymous with Vitamin E, but also for methyl tocols.

In the present application, by the terms tocopherol, tocotrienol and derivatives thereof we include all compounds that exhibit the general physiological activity of Vitamin E. Thus, we include, inter alia, the α-, β-, γ- and δ- forms of tocopherol and tocotrienol that differ by the

number and position of methyl groups on the chromanol ring as well as the various isomers of these compounds. By derivatives of tocopherol and tocotrienol we are referring to the pharmaceutically acceptable derivatives, such as the esters of tocopherol, e.g. the linoleate, nicotinate, acetate or acid succinate ester.

In the present composition, a mixture of two or more compounds selected from tocopherol, tocotrienol and the derivatives thereof may be used.

A preferred compound for use in the emulsions of the present invention is α-tocopherol (also known as all-rac-α-tocopherol) as described in the United States Pharmacopoeia, Volume 23, 1995. A pharmaceutical grade can be obtained from Roche Products, Heanor, UK.

By a short chain phospholipid we particularly mean a phospholipid that contains two acyl functions where each acyl function has a carbon chain length of 14 or less. Such short chain phospholipids have been described in US-5,179,079. They have not been used previously to solubilize and disperse immunosuppressant drugs.

By the term "phospholipid", we include both phospholipids and lysophospholipids or mixtures thereof.

Suitable phospholipids for use in the present composition include, inter alia, dioctanoyl-L-α-phosphatidylcholine, dioctyl-O-L-α-phosphatidylcholine, didecanoyl-L-α-phosphatidylcholine, didecyl-O-L-α-phosphatidylcholine, decyl-O-L-α-lysophosphatidylcholine, dilauroyl-L-α-

phosphatidylcholine, lauroyl-L-α-lysophosphatidylcholine or any other phospholipid mentioned in US-5,179,079.

In a preferred embodiment, the short chain phospholipid is didecanoyl-L-α–phosphatidylcholine (DDPC) (which can be obtained from the Natterman Company in Germany). DDPC is preferred over other short chain phospholipids because it is oily in nature and is well miscible with Vitamin E. Mixtures of two or more phospholipids may be used if desired.

Suitable non-ionic surfactants for use in the present invention include, inter alia, polysorbate 80 (Tween 80), polyoxyethylene castor oil derivatives (e.g. Cremophor EL), pharmaceutically acceptable block copolymers, such as poloxamines or poloxamers, polyoxyl 40 hydrogenated castor oil, polyoxyl 10 octyl ether, polyoxyl 8 stearate, polyoxyl 40 stearate, polysorbates 20, 40, 60 ,65, 80 and 85, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan sesquioleate, sorbitan trioleate and sorbitan tristearate. Mixtures of two or more non-ionic surfactants may be used if desired.

The composition of the invention typically comprises from 5 to 85 % by weight of the Vitamin E, tocotrienol or derivative, from 1 to 80 % by weight of the phospholipid, from 5 to 85 % by weight of the non-ionic surfactant and from 1 to 40 % by weight of the immunosuppressant. In a preferred embodiment, the composition comprises from 20 to 80 % by weight, particularly from 35 to 80 % by weight of the Vitamin E, tocotrienol or derivative, from 2 to 60 % by weight, particularly from 5 to

40 % by weight of the phospholipid, from 5 to 70 % by weight, particularly from 5 to 50 % by weight of the non-ionic surfactant, and from 5 to 30 % by weight, particularly from 5 to 20 % by weight of the immunosuppressant.

The present invention is now illustrated but not limited with reference to the following examples. In each example, the cyclosporin was dissolved in α-Tocopherol (Vitamin E) together with the short chain phospholipid and the non-ionic surfactant.

Example 1 **Preparation of a Mixture of Vitamin E and DDPC**

α-Tocopherol (Vitamin E) was obtained from Sigma (Poole, UK). Didecanoyl-L-α–phosphatidylcholine (DDPC) was obtained from Novo Nordisk (Denmark). 200 mg of DDPC was stirred into 2 g of the α-Tocopherol. The mixture was stirred for 4 hours at 30-40°C. A clear yellow coloured solution was produced.

Example 2 **Preparation of Mixtures of Vitamin E, DDPC and a non-ionic surfactant.**

A series of formulations having the compositions shown in Table 1 were prepared as described below. The surfactants Tween 80 (Polysorbate 80) and Cremophor EL (polyoxyl 35 castor oil) were selected. Both of these have been approved for use in oral pharmaceutical products.

DDPC was added to the α-tocopherol (Vitamin E) in a 10 ml vial and the contents stirred at 30-40°C until the DDPC had dissolved. Tween 80 or Cremophor EL was then added to the solution and mixed at 30-40°C. In order to test dispersibility, 5 ml of water was added into the vial and the vial shaken vigorously.

All the formulations were transparent, oily liquids with a yellow/brown colour and formed O/W (oil in water) emulsions after mixing with water. Tween 80 was found to be better than Cremophor EL both in reducing the viscosity of the oily solution and in forming an O/W emulsion. Increasing the amount of Tween 80 reduced the viscosity of the formulation. All emulsions were milk-like with a light yellow/brown colour. The emulsions containing Tween 80 were less viscous than those containing Cremophor EL.

Table 1

Composition	Formulation							
	1	2	3	4	5	6	7	8
Vitamin E (g)	1	1	1	1	1	1.1	1.2	1.4
DDPC (g)	-	-	0.1	0.1	0.2	0.2	0.2	0.2
Tween 80 (g)	0.5	-	0.1	-	0.6	0.5	0.4	0.2
Cremophor EL (g)	-	0.5	-	0.1	-	-	-	-

Example 3 **Incorporation of Cyclosporin in Vitamin E**

200 mg of cyclosporin was mixed with 1 g of α-tocopherol (Vitamin E) and stirred at 30-40°C for approximately 48 hours. A transparent, very viscous solution was obtained. The solubility of cyclosporin in Vitamin E was at least 200 mg/g.

Example 4 **Preparation of Formulations of Cyclosporin in Vitamin E with DDPC and Tween 80**

Formulations containing from 100 mg to 200 mg of cyclosporin and having the compositions shown in Table 2 were prepared in a unit dose quantity as described below.

Cyclosporin was added to α-tocopherol (Vitamin E) in a 10 ml vial and then stirred at 30-40°C until the cyclosporin had dissolved. DDPC was added into the vial and stirred at 30-40°C until the DDPC had dissolved. Tween 80 was then added into the vial and the contents mixed. In order to test for the dispersibility of the formulation in an aqueous environment such as that found in the gastrointestinal tract of a mammal, 5 ml of water was added into the vial and the vial shaken vigorously using a vortex mixer.

Table 2

Composition	Formulation				
	1	2	3	4	5
Cyclosporin (g)	0.1	0.1	0.15	0.2	0.2
Vitamin E (g)	1.0	1.0	1.0	1.0	1.0
DDPC (g)	0.1	0.2	0.2	0.5	0.1
Tween 80 (g)	0.1	0.1	0.2	0.3	0.7
Dose (mg/mg of Cyclosporin in Formulation)	1/13	1/14	3/31	1/10	1/10

Results

1. The final solutions 1-5 were transparent and yellow in colour.

2. The viscosities of the solutions were Formulation 1:+++; Formulation 2:+++; Formulation 3:++; Formulation 4: +++++; Formulation 5:+ (where increasing + indicates increasingly viscosity)

3. The times (in seconds) for forming an oil in water emulsion with 5 ml of water using the vortex mixer (speed 10) were as follows:

Formulation 1: 60 seconds

Formulation 2: 60 seconds

Formulation 3: 30 seconds

Formulation 4: 150 seconds

Formulation 5: 10 seconds

All formulations were transparent liquids with a yellow/brown colour and had free flowing properties at room temperature. All formulations formed well dispersed O/W emulsions when mixed with water to simulate the behaviour of the product in the gastrointestinal tract.

The liquid formulations described in this example can be filled into capsule systems familiar to those skilled in the art. Such capsules include hard and soft gelatin capsules and starch capsules as described in the United States Pharmacopoeia.

Claims:

1. A composition comprising (i) an immunosuppressant, (ii) at least one compound selected from tocopherol, tocotrienol and the derivatives thereof, (iii) a short chain phospholipid and (iv) a non-ionic surfactant.

2. A composition according to Claim 1, wherein the short chain phospholipid is a lysophospholipid.

3. A composition according to Claim 1, wherein the phospholipid is didecanoyl-L-α–phosphatidylcholine.

4. A composition according to any one of Claims 1 to 3, wherein the non-ionic surfactant is Polysorbate 80 or Polyoxyl 35 castor oil or a block copolymer in the form of a poloxamer or poloxamine.

5. A composition according to any one of Claims 1 to 4, wherein component (ii) is tocopherol.

6. A composition according to 5, wherein component (ii) is α-tocopherol.

7. A composition according to any one of Claims 1 to 6, wherein the immunosuppressant is a cyclosporin.

8. A composition according to any one of Claims 1 to 6, wherein the immunosuppressant is FK-506 or rapamycin.

9. A composition according to any one of Claims 1 to 9 which comprises from 5 to 85 % by weight of the Vitamin E, tocotrienol or derivative, from 1 to 80 % by weight of the phospholipid, from 5 to 85 % by weight of the non-ionic surfactant and from 1 to 40 % by weight of the immunosuppressant.

10. A composition according to Claim 9 which comprises from 35 to 80 % by weight of the Vitamin E, tocotrienol or derivative, from 5 to 40 % by weight of the phospholipid, from 5 to 50 % by weight of the non-ionic surfactant, and from 5 to 20 % by weight of the immunosuppressant.

11. A composition according to any one of Claims 1 to 10 which is in a form for oral delivery.

12. The use of a composition according to any one of Claims 1 to 11 in the manufacture of a medicament for treatment of a mammalian patient in need of immunosuppression.

13. The use of a composition according to any one of Claims 1 to 11 in the manufacture of a medicament for prevention of graft rejection following bone marrow, kidney, liver, pancreas, heart and heart-lung transplantation, and for prophylaxis of graft-versus-host disease.

14. A method of treating immunosuppression which comprises administering a composition according to any one of Claims 1 to 11 to a patient in need of such treatment.

15. A process for the preparation of a composition according to any one of Claims 1 to 11 which comprises mixing the components together.